Efficacy of non-invasive respiratory support modes for primary respiratory support in preterm neonates with Respiratory Distress Syndrome: Systematic review and network meta-analysis.

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Abstract

Objectives: To compare the efficacy of different non-invasive respiratory support modes for primary respiratory support of preterm infants with Respiratory Distress Syndrome (RDS). Design: Systematic review and network meta-analysis using the Bayesian random effects approach. MEDLINE, EMBASE and CENTRAL were searched. Interventions : HFNC (High Flow Nasal Cannula), CPAP (Continuous Positive Airway Pressure), BiPAP (Bilevel CPAP), NIPPV (Non Invasive Positive Pressure Ventilation). Main outcome measures: Requirement of invasive mechanical ventilation, any treatment failure. Results: 34 studies including 3994 patients were included. NIPPV was more effective in decreasing the requirement of mechanical ventilation than CPAP {RR [95% Credible Interval (CrI)] - 0.60 (0.44, 0.79)}and HFNC [0.66 (0.43, 0.99)]. Surface under the cumulative ranking curve (SUCRA) for NIPPV, BiPAP, HFNC and CPAP were 0.94, 0.59, 0.32 and 0.13. For the outcome of treatment failure, both NIPPV and BiPAP were more efficacious compared to CPAP and HFNC {0.56 (0.44, 0.71) [NIPPV vs CPAP], 0.69 (0.51, 0.93) [BiPAP vs CPAP], 0.42 (0.30, 0.63) [NIPPV vs HFNC], 0.53 (0.35, 0.81) [BiPAP vs HFNC]}. The SUCRA for NIPPV, BiPAP, CPAP and HFNC were 0.96, 0.70, 0.32 and 0.01. NIPPV was associated with a reduced risk of air leak compared to BiPAP and CPAP [0.36 (0.16, 0.73); 0.54(0.30, 0.87), respectively]. NIPPV resulted in lesser incidence of BPD or mortality when compared to CPAP [0.74 (0.52, 0.98)]. Nasal injury was lesser with HFNC compared to CPAP [0.15 (0.01, 0.60)]. Conclusions: Most effective primary mode of non-invasive respiratory support in preterm neonates with RDS was NIPPV.

INTRODUCTION

The introduction of surfactant had a major impact in improving the outcomes of preterm neonates with RDS[1].There was a major shift in the practice of surfactant therapy in the last decade with studies showing better outcomes with early selective rescue treatment when compared to the previously practiced prophylactic administration[2]. Stabilising neonates with RDS on a non-invasive respiratory support (NRS) such as CPAP and then instituting surfactant therapy in selective neonates who have an increased oxygen requirement has become the standard practice[3]. Newer modalities of NRS strategies that have come into practice in neonatal medicine in the past two decades, include heated and humidified high flow cannula (HFNC), non-invasive positive pressure ventilation (NIPPV), bilevel CPAP (BiPAP) as well as nasal high frequency oscillation ventilation (nHFOV)[4,5].

Several systematic reviews compared different NRS strategies in pair-wise meta-analysis, however only one network meta-analysis (NMA) evaluated different NRS strategies in preterm neonates with RDS[6-10]. The

NMA by Isamaya et al. also included different modalities of surfactant instillation [Less Invasive Surfactant Administration (LISA), Intubate Surfactant and Rapid Extubation (INSURE) and mechanical ventilation following surfactant] along with CPAP and NIPPV[10].

In this systematic review, we critically review the different modes of NRS and compare their effects in a NMA .

METHODS

The efficacy and safety of four NRS modalities used as primary respiratory support in preterm neonates with RDS were compared: HFNC, CPAP, BiPAP and NIPPV. The systematic review protocol was registered with PROSPERO (CRD42020177474)[11]. The reporting of this review is consistent with the PRISMA for network meta-analyses guidelines[12].

Types of studies

Only randomized controlled trials (RCTs) that have compared the four different NRS treatments (HFNC, CPAP, BiPAP and NIPPV) were included. Studies published as peer reviewed abstract form as well as non-english language studies were included in the final synthesis. Neonates with gestational age < 37 weeks with a primary diagnosis of RDS and who were started on a NIV support within the first 24 hours of life. Neonates who had received surfactant via standard practice (INSURE or LISA) prior to randomisation were included.

Outcomes

The primary outcomes were: 1) Requirement of invasive mechanical ventilation (MV) within the first 7 days of randomisation; 2) treatment failure, defined as requirement of an additional form of respiratory support for various reasons such as respiratory acidosis, hypoxemia or severe apnea within the first 7 days of randomisation. The secondary outcomes included incidence of mortality (neonatal and before discharge), incidence of Bronchopulmonary dysplasia (BPD) defined as oxygen requirement at 36 weeks of post menstrual age, incidence of mortality or BPD, incidence of air leak, incidence of severe IVH defined as Grade > 2[13], incidence of NEC stage $>/= 2$[14], incidence of PDA requiring medical therapy or surgical intervention, incidence of severe ROP defined as those requiring laser therapy and or intra-vitreal anti-vascular endothelial growth factor (VEGF) and / or stage $>/= 3$ as per ICROP[15] and incidence of nasal injury.

Search methods for identification of studies

Three electronic databases were searched, namely MEDLINE via Pubmed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from their inception till 29th March 2020. The search strategy that was used is provided in the **E-Table 1** .

Selection of studies

Two authors (VVR and PBH) independently reviewed the abstracts of the search results. Full texts of the eligible articles were extracted by the two review authors for further evaluation. In case of any conflicts, a third author's (KM) opinion was sought.

Assessment of risk of bias in included studies

The Cochrane risk of bias tool version 1 was used to assess the risk of bias of the included studies by two review authors independently (VVR and KM)[16]. The risk of bias was evaluated based on the following five domains - selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Any disagreement between the reviewers was resolved by discussion or consultation with the third author (PBH).

Data synthesis

The characteristics of the included studies were tabulated and reviewed to exclude those studies that might result in intransitivity. Network meta-analysis was done by Bayesian approach using a random effects model with Markov chain Monte Carlo simulation with vague priors (*GEMTC, BUGSnet)* using the R-software

(Version-R 3.6.2)[17,18]. Generalised linear models with 4 chains, burn-in of 50,000 iterations followed by 100,000 iterations with 10,000 adaptations was used[18].The geometry of the networks were assessed using network plots with the size of the nodes being proportional to the number of subjects included in the intervention and the thickness of the arms connecting the different intervention nodes corresponding to the number of studies included in the comparison. Model convergence was assessed using Gelman-Rubin plots as well as by analysing the trace and density plots[19]. Inconsistency was assessed by node-splitting[20]. Pair-wise meta-analysis evaluating the direct evidence for the different NIV modalities was also done and heterogeneity was assessed using I^2 statistic and Cochran Q test. The results of the network meta-analysis were expressed as risk ratios (RR) with 95% credible intervals in league matrix tables and forest plots. The league matrix tables display the RR of the outcome parameter for the intervention in the row versus that in the column in the lower triangle and vice versa in the upper triangle. The comparison of direct and indirect evidence using node-splitting are expressed as odds ratios (ORs) with 95% credible intervals. Surface under the cumulative ranking curve (SUCRA) was used to rank interventions for all the outcomes. SUCRA is an index with values from 0 (least effective intervention) to 1 (best intervention)[21]. SUCRA should always be interpreted with 95% credible intervals as well as the quality of the evidence. The confidence in the final estimates for all the outcomes were assessed using GRADE approach as recommended by the GRADE working group[22].

Meta-regression and Sensitivity analysis

Meta-regression was done using age as the covariate. Two sensitivity analyses were done - excluding trials with high risk of bias and those that had enrolled neonates who had already received surfactant prior to randomisation.

Results

The electronic database search revealed a total of 9032 studies. After screening for suitability, 34 studies were included in the final synthesis [23-56]. The PRISMA flow diagram is depicted in **Figure 1** . Thirty-three studies (3994 neonates) and 31 studies (3783 neonates) were analysed for the primary outcomes of treatment failure and requirement of mechanical ventilation, respectively. The mean gestational age of the neonates was 31 weeks (**E-Figure 1).** Five studies had enrolled neonates who had already received surfactant prior to randomisation. The time cuts-offs for treatment failure and mechanical ventilation was within the first 72 hours after randomisation for most of the included studies. The characteristics of the included studies are given in **Table 1** .

Risk of bias assessment of included studies

Overall, twelve studies [25, 28, 30, 32, 33, 37, 40, 41, 42, 43, 50, 56] were regarded as having a low risk of bias, the remaining studies were found to have variable degrees of risk of bias. Thirteen studies had high risk of bias [34, 35, 36, 38, 44, 46, 47, 48, 49, 51, 53, 54, 55] with issues in randomisation and / or allocation concealment. Six studies [23, 24, 29, 39, 45, 52] had unclear bias as methodology was not described very well. One study was adjudged to have high risk of bias for selective outcome reporting due to early stoppage of the trial [27]. The risk of bias of the included studies is depicted in **E-Figure 2.**

Primary Outcomes

Requirement of mechanical ventilation

A total of 31 studies enrolling 3783 neonates with 669 events in the network was analysed (**Figure 2, Table 2).** Inconsistency assessed by node-splitting for all the outcomes is illustrated in**E-Figure 3** and **E-Figure 4** . In comparison with HFNC, only NIPPV showed a statistically significant reduction in the requirement of MV [0.66 (0.43, 0.99)]**(Figure 3)** . Also, NIPPV was more effective in decreasing the risk of MV intubation when compared to CPAP [0.60 (0.44, 0.79)]. The league matrix is given in**Table 3** . SUCRA for NIPPV, BiPAP, HFNC and CPAP were 0.94, 0.59, 0.32 and 0.13 respectively making NIPPV the best initial mode of NRS and CPAP the least effective (**Figure 4)** . Meta-regression with gestational age as covariate showed a trend of improving efficacy of HFNC in reducing the risk for mechanical ventilation with increasing gestational age when compared to NIPPV, BiPAP and CPAP (**E-figure 5)** . The pairwise comparison of different NRS

interventions evaluating the direct evidence for the primary outcomes is illustrated as forest plots in **Figure 5.**

Treatment failure

A total of 33 studies enrolling 3994 neonates with 678 events in the network were analysed (**Figure 2, Table 2).** Both NIPPV and BiPAP were associated with lesser risk of treatment failure when compared to HFNC [0.42 (0.30, 0.63) and 0.53 (0.35, 0.81), respectively] and CPAP [0.56 (0.44, 0.71) and 0.69 (0.51, 0.93) respectively] (**Figure 3, Table 3)** . The SUCRA for NIPPV, BiPAP, CPAP and HFNC were 0.96, 0.70, 0.32 and 0.01 respectively. **(Figure 4)** . Meta-regression showed a trend similar to the outcome of mechanical ventilation. **(E-Figure 6)** .

Secondary Outcomes

The geometry and other characteristics of the networks for the different secondary outcomes are displayed in **Figure 2 / E-Figure 7 and Table 2,** respectively**.** The network assessing the outcomes mortality and NEC were inconsistent as assessed by node-splitting. The SUCRA plots for the secondary outcomes are given in the **Figure 4 / E-Figure 8.**

Air leak

NIPPV was associated with lesser incidence of air leak when compared to both CPAP [0.54 (0.30, 0.87)] and BiPAP [0.36 (0.16, 0.73]**(Figure 3 / Table 3)** .

Mortality

NIPPV decreased the risk of mortality when compared to CPAP [0.60 (0.37, 0.89)] and BiPAP [0.48 (0.22, 0.95)] **(Figure 3 / Table 3)** .

Mortality or BPD

NIPPV was associated with a decreased risk of the combined outcome of BPD or mortality when compared to CPAP [0.74 (0.52, 0.98)]**(Figure 3 / Table 3)** .

Nasal Trauma

HFNC resulted in reduced incidence of nasal injury when compared to CPAP [RR - 0.15 (0.01, 0.60)] **(E-Figure 9/ Table 3)** .

Sensitivity analysis

Excluding studies with high risk of bias

When studies with high risk of bias were excluded, there was no difference in efficacy between any of the NRS modalities for the outcome MV. The results were unchanged for other outcomes (**E-Figure 10 and E-Figure 11).***Excluding studies which had enrolled neonates who had already received surfactant*The results were unchanged after excluding trials that had enrolled neonate who had already received surfactant prior to randomisation

(E-Figure 10 and E-Figure 11).

Quality of Evidence

The overall confidence in the NMA effect estimate for the primary outcomes of treatment failure and requirement of mechanical ventilation was moderate for HFNC vs CPAP ; CPAP vs NIPPV comparisons and low to very low for other comparisons. The quality of evidence was low to very low for all other secondary outcomes for the different comparisons. The GRADE table is given in **Table 4** .

Discussion

This network meta-analysis included data of 3994 preterm babies from 34 studies to evaluate the efficacy of different NRS modalities as primary support for RDS. Clear differences between NRS modes were found. NIPPV reduced the risk of MV when compared to both CPAP and HFNC. Also, both NIPPV and BiPAP were associated with lesser treatment failure in comparison to CPAP and HFNC. Ranking probabilities indicate that NIPPV might be the most appropriate primary modality of NRS in preterm neonates with RDS.

The findings of this network meta-analysis are similar to Lemyre et al's with NIPPV being superior to CPAP in preventing treatment failure as well as MV[9]. The relative risk reduction for both the primary outcomes were much larger than that reported by Lemyre et al. with narrower credible intervals. Reasons for this could be that this network meta-analysis had included more recently published studies and also that the modalities BiPAP and NIPPV were evaluated as separate interventions. Also, this was a network meta-analysis where apart from the direct synthesis, the indirect evidence also contributed towards the overall effect estimate. It is evident from the included studies that the peak inspiratory pressure (PIP) and hence the mean airway pressure (MAP) that was delivered with NIPPV was much higher than the positive end expiratory pressure (PEEP) generated with CPAP[41-53]. This might be one of the reasons for NIPPV being more effective than CPAP. The fact that the incidence of air leak as well as that of the combined outcome of BPD or mortality was much lesser with NIPPV when compared to CPAP might suggest that the use of a relatively higher MAP with NIPPV was not deleterious.

The results of this NMA were similar to those by Fleeman et al. and Hong et al. with HFNC being equally efficacious as CPAP as a primary mode of respiratory support in neonates with RDS[7,8]. It should be noted that most of the studies that had compared HFNC with CPAP had enrolled neonates of gestational ages of more than 28 weeks. Hence, these findings are not generalisable to the more immature neonates. The meta-regression also showed a trend of HFNC being less efficacious at lesser gestational ages compared to other NRS modalities. However, the results were imprecise making it difficult to draw reasonable conclusions.

Both NIPPV and BiPAP were equally efficacious in preventing treatment failure and mechanical ventilation. Most of the evidence that contributed to this comparison was indirect and there was only a single RCT that had compared these two interventions[56]. Millar et al. in their *a priori* planned non-randomised comparison of neonates randomised to the NIPPV arm of the NIPPV trial (a large RCT comparing NIPPV/BiPAP versus CPAP as primary as well as post extubation respiratory support) had reported similar findings with no differences in the incidence of re-intubation between NIPPV and BiPAP groups in the first week after randomisation in the primary respiratory support group[57]. Similar to the BiPAP versus NIPPV comparison, there was paucity of direct evidence for studies evaluating HFNC versus NIPPV where only two RCTs contributed to the direct evidence[54,55]. These reiterate the need for further RCTs comparing these interventions.

The analysis of secondary outcomes reveal that both BiPAP and CPAP were associated with an increased risk of air leak and mortality when compared to NIPPV. Also, the risk of mortality or BPD was higher in CPAP compared with NIPPV. Isayama et al. in their network meta-analysis of different invasive and non-invasive modalities along with different methods of surfactant administration in preterm neonates with RDS had found no differences in the incidence of air leak, mortality or BPD between CPAP and NIPPV[10]. This discrepancy between this network meta-analysis and Isayama et al.'s might be due to the fact that this network meta-analysis had included only non-invasive modalities of respiratory support and had excluded neonates requiring invasive MV. Also, more recent studies that were published after Isayama et al's meta-analysis were included in the present analysis[39,40,51-53]. It should be noted that the network assessing the outcome mortality was inconsistent. In a scenario where inconsistency has been detected for an outcome in a network meta-analysis, the network estimates are not reliable and any changes in the included studies to address the inconsistency becomes a *post hoc* analysis[58].

The increased risk of air leak with BiPAP when compared to NIPPV could be explained by the different mechanism of flows used by these two interventions[59].While NIPPV uses a fixed flow using a ventilator, BiPAP is a variable flow device. Some of the BiPAP studies have used very high Pressure high of upto 15

cm H2O which might require a very high gas flow rate[60]. Also, the inspiratory times are typically higher in BiPAP compared to NIPPV which might result in the alveoli being exposed to higher pressures for a longer period of time as well as increasing the risk gas trapping, especially when higher respiratory rates are used. The risk of mortality or BPD was higher in CPAP compared with NIPPV in this network meta-analysis. This was not seen in the Isayama et al's network meta-analysis. This might be due to the differences in the inclusion criteria between the two meta-analyses as specified above. Also, the quality of evidence for most of the secondary outcomes of this network meta-analysis were low to very low and hence should be interpreted with caution.

Strengths and Limitations

This is one of the largest network meta-analysis evaluating the different NRS modalities used as primary support for preterm neonates with RDS. It is PRSIMA network meta-analysis extension compliant. The quality of evidence for all the outcomes was done in a very robust manner as per the GRADE working group recommendations.

Limitations in this network meta-analysis include that this did not include two of the recently introduced NRS modalities in neonatal respiratory care namely, nasal high frequency oscillation ventilation (nHFOV) and neurally adjusted Ventilatory assist (NAVA). Also, two of the secondary outcomes (NEC and Mortality) had inconsistent networks. Finally, the event rates and the optimal information size for most of the secondary outcomes were low with the quality of the evidence being downgraded to low to very low for these outcomes.

Conclusions

The overall quality of evidence for the primary outcomes was moderate to very low for the different comparisons. NIPPV appears to be the most effective primary NRS modality in preterm neonates with RDS to prevent MV and respiratory failure in the first few days of life.

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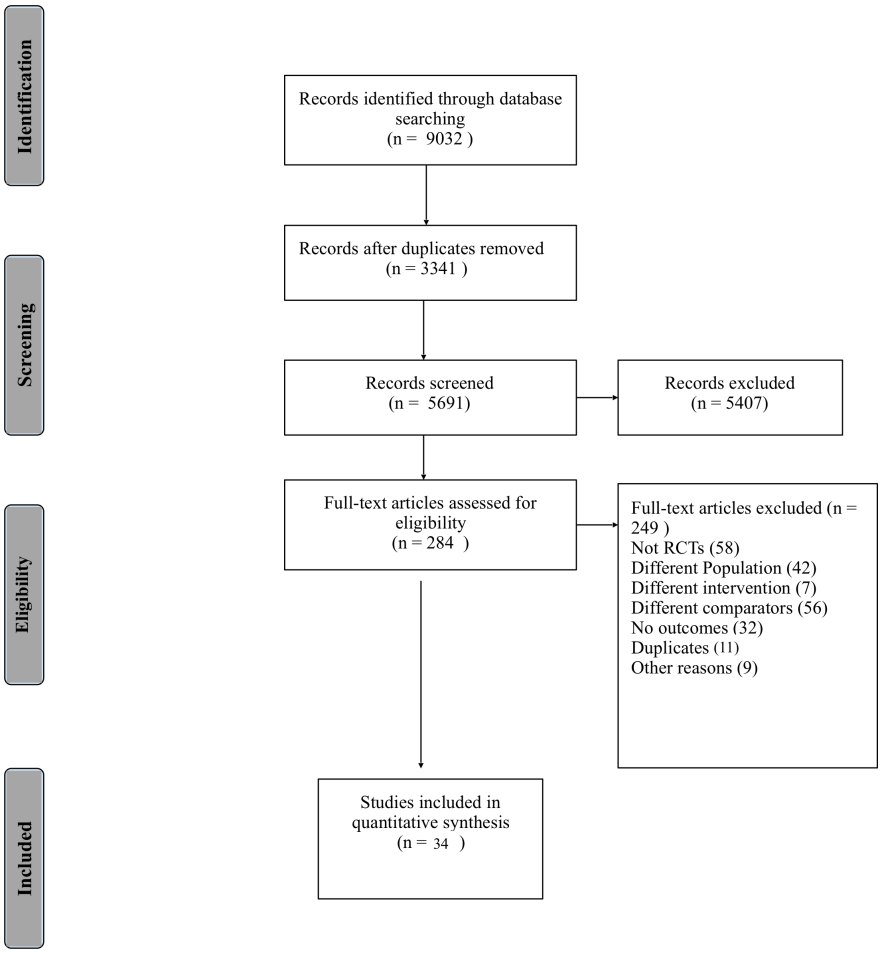
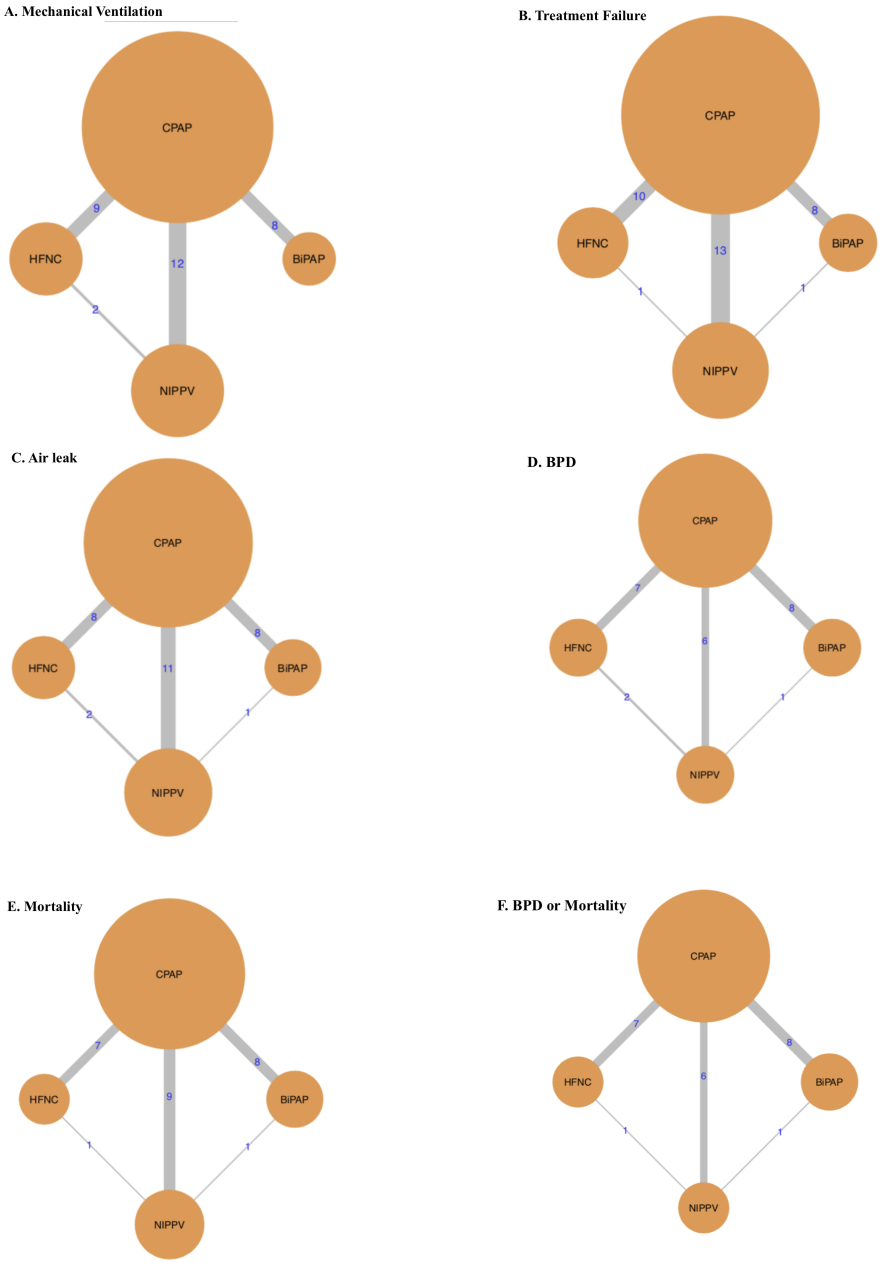
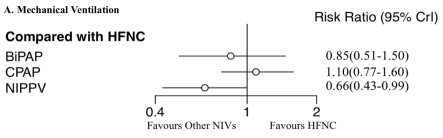
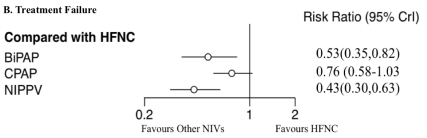
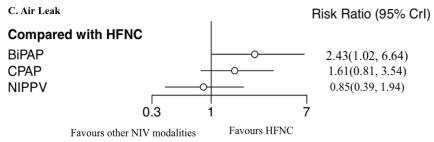
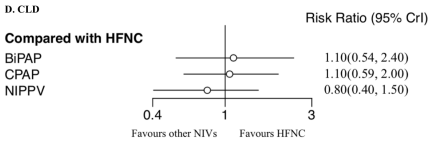


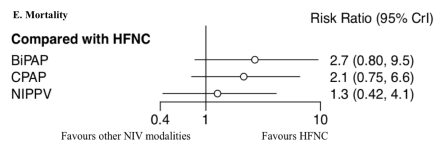


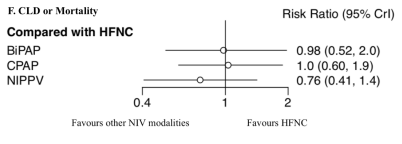


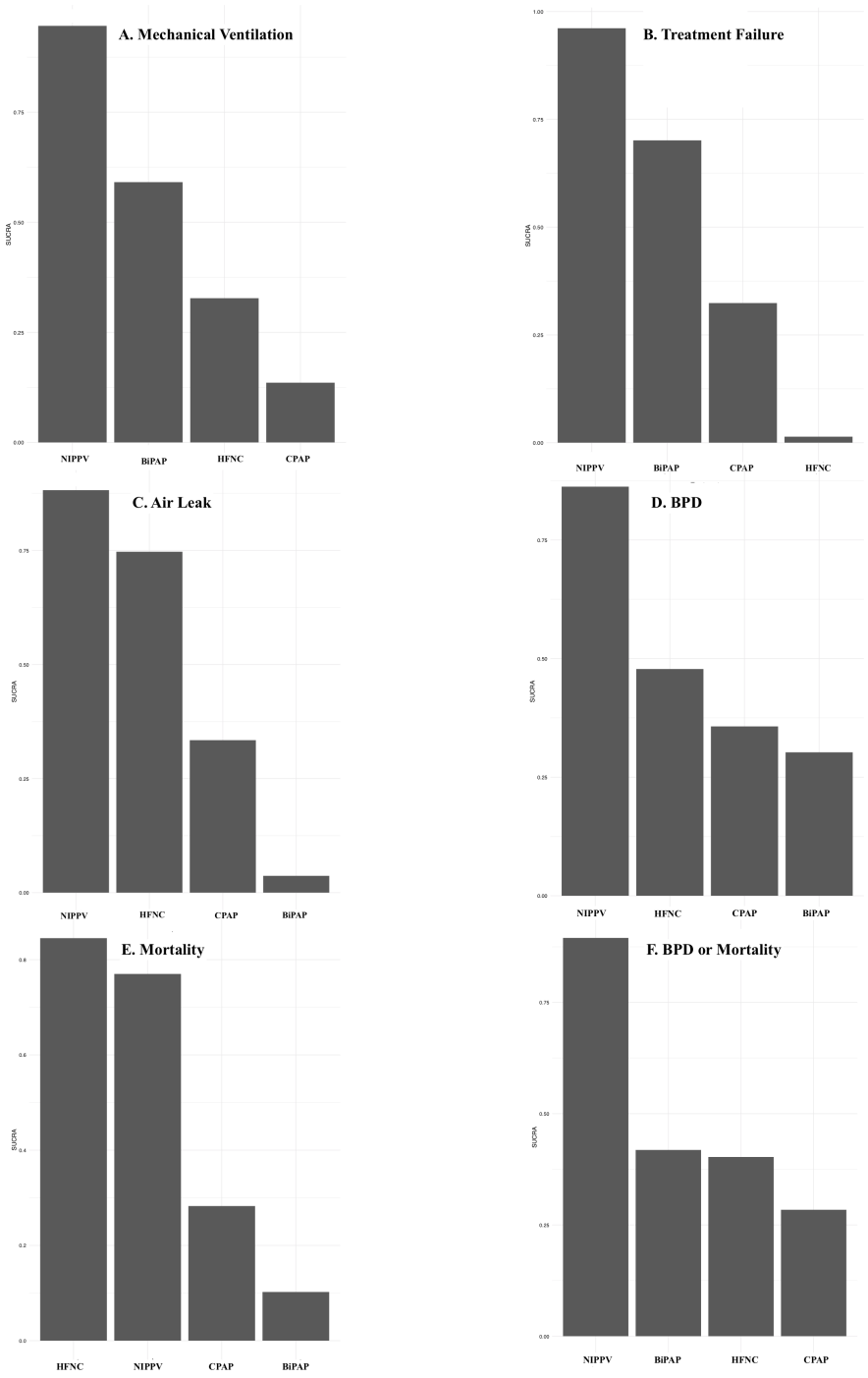




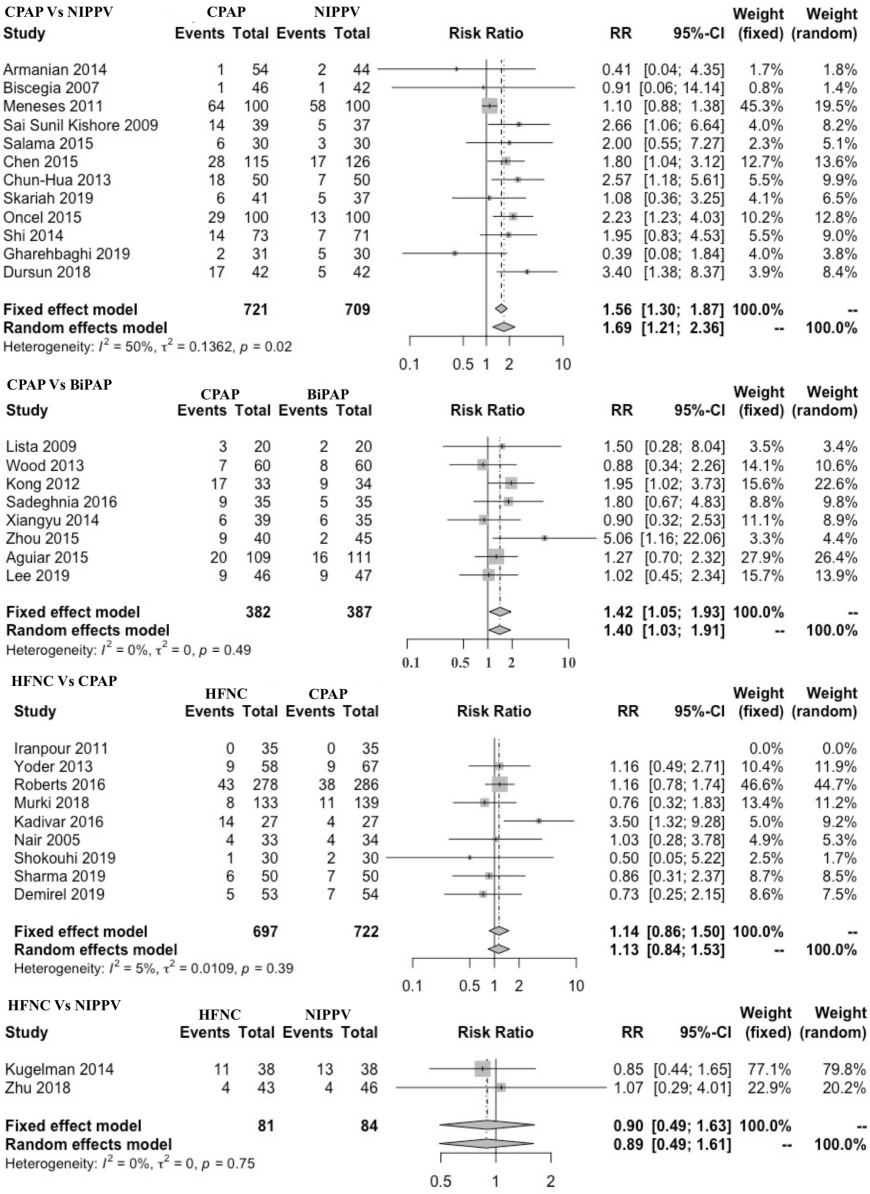








Primary Outcome - Mechanical Ventilation - Pairwise meta-analysis



Primary Outcome - Treatment Failure - Pairwise meta-analysis